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Delayed Resection in the Management of Non-Orbital Rhabdomyosarcoma of the Head and Neck in Childhood

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This retrospective study was undertaken to evaluate the effect of delayed resection on outcome of head and neck rms in a single institution which has experience in cranial base surgery. Since 1988, patients with primary non-orbital rms of the head and neck following treatment at the Children's Hospital of Pittsburgh, were evaluated by the Department of Otolaryngology, Eye and Ear Hospital at the University of Pittsburgh Medical Center either at the time of presentation or when response to chemotherapy and/or radiation therapy was thought to have been optimized for the possibility of definitive surgery. Medical records of patients who did or did not have delayed surgery were reviewed and compared with respect to demographics, tumor stage, response to therapy, survival, and cosmetic results. Of 16 children diagnosed with non-orbital head and neck rms from 1988–1994 and treated with chemotherapy according to IRS II-IV, 3 had group I or II disease following extensive surgery at diagnosis. Thirteen had group III or IV disease. Of these, 6 patients had delayed resection and 7 did not. Delayed resection was undertaken 3–12 months (median, 4 months) from diagnosis in 4 children who had a partial response (PR) and 2 children who had stable disease (SD) with chemotherapy and/or radiation. Delayed resection converted all children to complete responses (CR), including one child with clinical SD and one with PR who were found to have no viable tumor at surgery. The overall percentages of CRs for patients with group III or IV disease (documented any time post-diagnosis) were at least as good for patients who had undergone delayed surgery as for those who had not (100% vs. 71%, p = .465). Median survivals for patients with advanced disease were 3½ years and 2 years, respectively (p = .2801). Cosmetic and functional problems attributable to surgery were not severe but included facial asymmetry (n = 4), trismus (n = 1), cranial nerve deficits (n = 1), and abnormal dentition (n = 1). In locally extensive head and neck rms, cranial base surgery should be considered after initial cytoreductive therapy, since it may contribute to achievement of CR and to survival with acceptable morbidity. **Med. Pediatr. Oncol. 28:294–298.**

Key words: rhabdomyosarcoma; cranial base surgery; head and neck

INTRODUCTION

A major determinant of outcome for children with rhabdomyosarcoma (rms) is stage of disease at diagnosis. Although improved disease-free survival (dfs) has been noted from 1978-1990, reflecting changes in treatment protocols from the Intergroup Rhabdomyosarcoma Study (IRS) I and II to IRS III, some 30–40% of patients with group 3 (gross loco-regional) disease still experience disease progression or recurrence [1,2]. Because of proximity to vital or functionally important structures, head and neck primaries often are not resected and therefore fall into advanced stage disease categories.

In IRS III, 75% of patients undergoing delayed surgery (''second look'' operations) following induction therapy for non-head and neck primaries, were either confirmed to be complete responses (CR) or converted to a higher response status [1,3]. Experience with delayed resection in head and neck primaries is limited [4,6].

Since 1988, children with head and neck rms treated at the Children's Hospital of Pittsburgh (CHP) have been evaluated by members of the Department of Otolaryngology and the Center for Cranial Base Surgery, University of Pittsburgh Medical Center, either at presentation

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TABLE I. Clinical Characteristics of Study Patients*

Patient	Age (yr) race, sex	Primary site	Stage	Rx chemo/peak cGy to primary	Best response (Pre-SLO)	Outcome (yr after dx)
Primary resection						
1	2 3/12 WF	TF	II	VA	CR	NED (7 1/2)
2	8 BM	Parotid	II	VAI, E, Adr	CR	lung mets (7/12), NED (6)
3	15 WF	Stenson duct	I	VIE	CR	NED (2 3/12)
Delayed resection						
4	1 3/12 WM	PP	III	VAC/4140^{H}	SD	NED (5)
5	2 1/12 WM	TF	III	VAC/2800	PR	† (1)
6	2 1/2 WM	NP	III	VAC/0	PR	PD (2), NED S/P BMT (1/2)
7	2 9/12 WM	PF	III	VAC/5040	PR	NED (5 2/12)
8	2 11/12 WM	ITF	III	VAI/5080	SD	† (1 4/12)
9	6 WM	ITF	III	VAc/0	PR	NED (5 1/2)
Biopsy or subtotal resection at diagnosis						
10	1/12 WM	PP	III	VAC/0	CR	† (3 9/12)
11	8 BiF	MS	III	VAC/5940^{H}	PR	† (3 1/2)
12	8 1/2 BF	Petrous	III	VAC/5940^{H}	NR	† (1 1/12)
13	8 1/2 WM	NP	III	VIE/5400	CR	AWD (2)
14	10 1/12 WM	Cheek	III	VAI/5940	CR	† (1 1/12)
15	11 WM	NP	III	VAC/5940^{H}	CR	NED (5 1/12)
16	8 BF	Scalp	IV	VAdrI/5940^{H}	CR	† (1 1/12)

*Abbreviations: slo = second look operation; PP = parapharyngeal space, TF = temporal fossa, NP = nasopharynx, PF = pterygoid fossa, ITF = infratemporal fossa, MS = maxillary sinus; NED = no evidence of disease, † = died, AWD = alive with disease; SDc = stable disease (based on clinical citeria), PR = partial response, CR = complete response, NR = no response, V = vincristine, A = actinomycin, I = ifosfamide, C = cytoxan (2.2 gm/m^2), c = cytoxan (1.2 gm/m^2), E = etoposide, Adr = adriamycin; ^{H} = hyperfractionation, W = caucasian, B = black, Bi = biracial (black/caucasian).

or when response to chemotherapy and/or radiation was thought to have been optimized. Based upon this experience, we reviewed the use of delayed resection in children with residual head and neck lesions. A comparison of institutional results with head and neck rms not treated with delayed surgery suggests that there is a role for this aggressive approach in carefully selected children.

MATERIALS AND METHODS

All patients treated at CHP 1988–1994 with non-orbital rms of the head and neck were identified through the institutional tumor registry. Pathology reports were reviewed to confirm the diagnosis and histopathology, and medical records were examined for primary tumor site, clinical staging according to the IRS, initial surgical procedure, treatment protocol, best clinical response (based upon physical examination, radiographic studies and nuclear scans, and defined according to IRS criteria) [1] to pre-surgical therapy, and long-term outcome (disease status as well as functional/cosmetic status). Some, but not all, patients were evaluated prospectively by the Department of Otolaryngology and the Center for Cranial Base Surgery. Those patients who had been so evaluated were monitored with ongoing consultation. For other patients cranial base surgery consultation was requested at a time when response to chemotherapy and/or radiation therapy was thought to have been optimized. Thus, delayed surgery was not performed at a fixed time point. Results of delayed surgery or reasons for not doing second surgeries were noted. One patient #6 (Table I) elected to undergo delayed resection at Denver Children's Hospital by Dr. V. Schramm, and results of that procedure were available to us. Percentages of CR and median survival in patients who did or did not undergo delayed resection were compared using Fisher's Exact Test and life table analysis.

RESULTS

From 1988–1994, 31 children with rms were followed at CHP. Of these, 16 had head and neck primaries other than the orbit. The clinical characteristics of these latter patients are shown in Table 1. Apart from the high percentage of patients with rms of the head and neck and the surprising number of Afro-American children, the demographics are similar to what has been reported for head and neck rhabdomyosarcoma by the IRS [1,2]. Ten of the

TABLE II. Cranial Base Surgery in Study Patients*

Pt	Procedure	Time Post Dx (months)	Pathology	Outcome
4	Gross total resection: lateral temporal bone resection, translocation facial nerve, temporalis muscle transposition	4 m	Focal tumor at margins	NED: moderate asymmetry of face, neck; dental caries
5	Gross total resection: infratemporal skull base approach; partial mandibulectomy, excision temporalis muscle	7 m	Tumor near margin	Local recurrence, distant metastases; moderate facial asymmetry secondary to surgery and tumor growth
6	Gross total resection: infratemporal skull base approach; transoral approach; temporalis transposition, partial maxillectomy, external sphenoethmoidectomy	4 m	Microscopic tumor: margins clear	Good local control; mild facial asymmetry
7	Gross total resection; partial mandibulectomy, maxillectomy; removal of ITF	3 m	Tumor at margin	NED; trismus, moderate facial asymmetry
8	Gross total resection: facial translocation approach; infratemporal skull base resection; temporalis transposition	12 m	No tumor present	Good local control; pulmonary, CNS mets; persistent moderate facial nerve palsy
9	Gross total resection; left temporalis approach: excision temporalis muscle, partial mandibulectomy	3 m	No tumor present	NED; mild facial asymmetry, S/P reconstructive surgery

*ITF = infratemporal fossa.

patients (#1–6,8,9,11,12) were first evaluated by one or more members of the Center for Cranial Base Surgery (CS, IPJ) at the time of presentation. In three of the 16 patients (#1–3), extensive resections were performed after initial biopsy had provided a tumor diagnosis. These patients were group I or II.

The other 13 patients had advanced disease (group III, n = 12; group IV, n = 1). In two patients (#10,14), there was gross residual disease despite extensive debulking procedures (performed by referring surgeons, not cranial base surgeons). The other 11 patients had biopsy only. Five of the patients with advanced disease (#5,8,12,13, 16) had bony erosion. All but two of the patients with advanced disease (#14,16) had parameningeal primary sites. Histopathology was embryonal in 13, alveolar in two (#10,11) and undifferentiated in one (#5).

Of the 13 children with advanced disease, 5 including the one child with bone marrow metastases, at diagnosis (patient #16) achieved clinical CR with chemotherapy and radiation therapy, and therefore, did not undergo delayed surgery. Two other children did not undergo delayed surgery because of parental refusal (n = 1) or unresectability (n = 1). Among those 7 patients, all but one received peak tumor radiation doses of more than 5,000 cGy. Only one patient in this group is alive without disease, one patient is alive with local disease progression, and median survival is two years (range 1 1/12–5 1/12+ years).

Six other patients with group III disease did undergo delayed surgery. Radiation doses in those patients ranged from 0–5,000 cGy (median, 3,500 cGy). Only two patients (#7,8) received radiation therapy to the primary tumor site before undergoing definitive surgery. One patient (#5) received radiation as a palliative measure after local tumor progression.

Details of delayed surgery in these children are described in Table II. In all 6 children, clinical partial responses (PR, $\geqslant$50% decrease in tumor volume) or stable disease (SD, no response or <50% decrease in tumor volume) were converted to CR with gross total resection of residual masses. In four of these patients, microscopic tumor was identified in the resected specimen, and in three of these, involved the margin of resection. In two children, the residual mass contained no viable tumor. Three patients have remained disease-free 5–5½ years post diagnosis and are presumably cured of their disease. Three of the 6 patients who had delayed resection developed recurrent disease, but in two cases this involved pulmonary metastases. One of the patients (#6) had a single lung metastasis resected, followed by autologous bone marrow transplant (BMT). He is alive and well two years from diagnosis and six months post BMT. The other two patients died. At autopsy one was found to have both local and distant disease. The other had central nervous system (CNS) metastases from a parameningeal primary. Thus, local control was maintained in five of six patients. Of seven patients who did not undergo delayed definitive resection, local control was maintained in only one. Of the six others, all had CNS extension with or without progression within the original tumor bed.

In this series, there was no mortality related to cranial base surgery. As shown in Table II, morbidity exclusively due to surgery included facial asymmetry (n = 2), trismus (n = 1), and facial nerve palsy (n = 1). In one other patient, both surgery and radiation contributed to facial asymmetry, and in another patient asymmetry was due both to surgery and tumor regrowth. Although none of the living patients in this group has reached his pubertal growth spurt, to date the asymmetries are subjectively mild or moderate. The oldest child has noticeable but mild hypoplasia of the involved temporal fossa following two reconstructive surgeries.

DISCUSSION

Delayed resection following chemotherapy or radiation is an approach which has been successful in the treatment of a number of solid tumors. The use of such ''second look operations'' in rhabdomyosarcoma was built into the design of IRS III for children with group III primaries. Preliminary results of IRS III have suggested that almost 75% of patients who still have residual masses after chemotherapy can be converted to complete responders [1,3]. In that study, the application of delayed definitive resection to head and neck tumors was limited. Several small series of selected patients have suggested that oncologic cranial base surgery results in improved outcome with acceptable cosmetic results [4–6].

The results of the present study confirm that aggressive cranial base surgery can benefit children with head and neck rms. Three of our patients had extensive lesions which were shown by biopsy to be rms and were resected completely or with microscopic residual disease prior to initiation of chemotherapy. These children then received less intensive chemotherapy and either no radiation or radiation therapy in lower doses than had they been for group III. All are well, and as is the case for 83% and 77% of group I and II rms at other sites [1], are presumably cured of their cancer.

Six other children had delayed surgery. In 4 of these cases, partial responses to chemotherapy with or without radiation therapy increased the likelihood of definitive resection with minimal morbidity; in two cases, surgery was undertaken, despite less than 50% tumor shrinkage (i.e., less than PR) by chemotherapy and/or radiation therapy, as the best or only way of achieving a CR. In all cases, delayed surgery was successful in producing gross total resection. Although tumor was present at the margin in three patients, long term local control was excellent in five out of 6 patients. Two patients in this group died of progressive disease, and one patient is alive, status post autologous bone marrow transplant for distant recurrence. Median survival is 3½ years in this group of patients.

These results, while not statistically significant, compare favorably with those in our group III and IV patients who, for one reason or another, did not have delayed surgery. CR rates and median survival in that group were only 71% and 2 years, respectively. In this small series, the two groups were not strictly comparable. The non-surgery patients had a wider age range and different sex distribution. An unexpected finding was that four of the patients were Afro-American. The racial distribution among patients with head and neck rms was not commented upon in one report from the IRS [2]. This observation may deserve additional attention for possible epidemiologic significance, particularly given the prior observation by one of us that there is overrepresentation of Afro-Americans among children with another head and neck cancer, nasopharyngeal carcinoma [7]. In any case, the sample size is too small for multivariate analysis. However based upon IRS results, none of these variables should have had a major impact on the outcome [8]. The two features with the greatest prognostic significance, primary site, and group or stage were similar, in the two groups, as was the predominance of favorable histology. In particular, parameningeal sites (middle ear, nasopharynx, infratemporal fossa, sinuses) which carry a high probability of local and central nervous system progression were evenly distributed. While one child in the non-surgical group had group IV disease, her exclusion from analysis would not have changed the overall conclusions.

It is possible that some of the patients would have done well without delayed surgical excision, such as the patients in whom pathology failed to identify tumor in the residual mass. However, it is unlikely that the delayed surgery group was biased in favor of patients who would have done well anyway, since the CR rate prior to delayed surgery [0%] was less than the CR rate in the non-surgery group: i.e., without delayed surgery, many patients would not have achieved CR. Conversely, outcome in the non-surgical group was not biased by inclusion of patients with less good responses to chemotherapy and radiotherapy: five of 7 patients had achieved CR without surgery; one other patient's tumor was felt to be resectable, but surgery was not done for other reasons (parental concern about cosmetic outcome).

A major reluctance to encourage delayed resection has resulted from concerns about cosmetic outcome. Several patients in our experience have had facial asymmetries resulting from surgery. However, follow-ups to date have demonstrated these to be subjectively mild or moderate rather than severe. Most of the children who had extensive procedures also had radiation to the tumor bed. Because the effects of radiation on bone and soft tissue growth may be delayed, it is most likely that morbidity will progress over time. Nonetheless most of the problems we have seen have been amenable to reconstructive therapy.

One anticipated benefit of delayed surgery would be a

decreased likelihood of developing second malignancies from radiation. This may be particularly important in children with head and neck primaries, since they appear to be at increased risk compared to patients with other primaries [9]. In general, surgery was radiation-sparing since two children received no radiation and the median dose was 3,500 cGy overall, compared with 5,940 cGy in the non-surgical group. The incidence of second malignancies is about 2% at ten years from diagnosis [9], with a greater risk at higher doses of radiation [10]. On the other hand, there are no major chemotherapy modifications for patients undergoing delayed surgery. Thus, the incidence of second malignancy secondary to chemotherapy would be expected to be comparable in the two groups, and about 2% by ten years [9].

CONCLUSIONS

We conclude that for head and neck rms, extensive cranial base surgery at diagnosis or after initial cytoreductive therapy is feasible and results are promising. A multidisciplinary approach which includes head and neck surgeons and plastic surgeons should be encouraged.

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